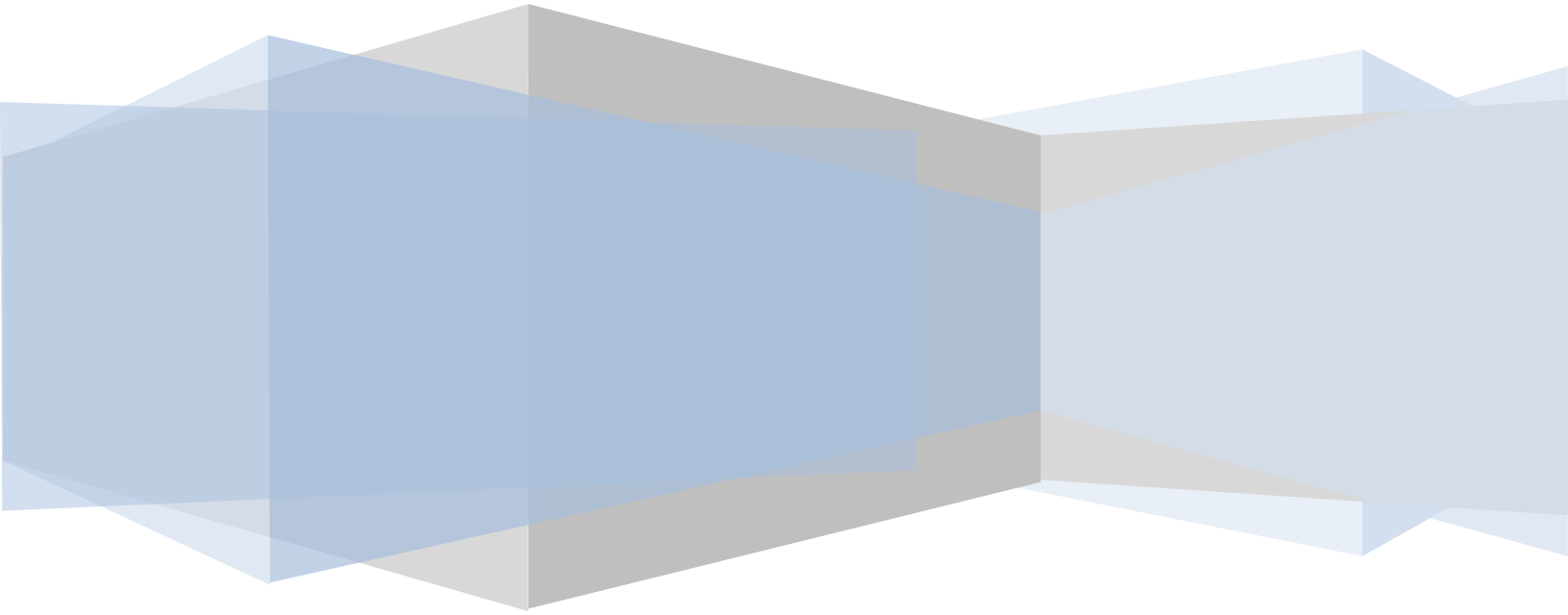
The International Pharmaceutical Excipients Council of the Americas

Inactive Ingredient Database Issues with ANDAs

BACKGROUNDER DOCUMENT

December 9, 2011



IPEC – FDA OGD Meeting – December 9, 2011

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BACKGROUNDER DOCUMENT

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Desired Outcome & Goals for the Meeting

IPEC Americas has been contacted by numerous member companies and other companies around the world (generic pharmaceutical companies and excipient manufacturers and distributors) during 2011 concerning issues they are having related to the manner in which FDA OGD has changed their policies regarding how the Inactive Ingredient Database (IID) is to be referenced in ANDA's to determine the precedence of use levels of specific grades of excipients in previously approved drugs.

New SRS related nomenclature has been used for specific grades and this has resulted in several IID references disappearing from the IID altogether which has caused many commonly used excipients to be treated like new excipients which require significant safety assessment. This has resulted in significant wasted resources on the part of the industry and the FDA to re-assess the safety of well-known excipients which do not have significant safety risks associated with their common uses. Appropriate ICH Q9 Risk Management concepts do not appear to be used during acceptance for filing reviews.

FDA did not clearly inform industry about the changes in policy that were being made and the way in which many companies found out about this was when they received a refuse to file or deficiency letter after filing their ANDA. This creates significant problems and delays in getting the ANDA reviewed and could even cause a company to lose First-to-File status.

IPEC Americas has requested the meeting to be held on December 9, 2011 to try to explain the concerns that this changed policy has created and to gain a better understanding of FDA OGD's needs so that Industry and FDA OGD can collaboratively develop an improved mechanism for using appropriate IID listing information to provide assurances of safety when using excipients that have been used in previously approved drugs.

Listed below are the key needs that IPEC would like to address during the meeting. IPEC Americas believes that these needs are reasonable and we hope that productive resolutions can be accomplished.

IPEC America's Needs

- **Utilize Maximum Potency levels previously used for generic family names when safety data covers the family of grades rather than specific levels listed for individual grades that are lower.**
- **Interim transitional process to minimize refuse-to-file letters when an ANDA uses a lower level of excipient than what was listed in previous versions of the IID.**
- **Clear mechanism to determine the appropriate nomenclature to be used in the IID for different grades of excipients (and mixtures) and to determine the appropriate IID maximum for ANDA references that cover these grades.**
- **A formalized process that includes public input on future deletions, consolidations and modifications of existing information in the IID prior to revision.**

- **Clear mechanism to supply additional safety information or bridging studies on a one-time basis when needed to support the safety of an entire family of excipients or for specific grades within a family of excipients if safety information may be different from grade to grade.**
- **There MUST be a mechanism for FDA to utilize the information in a Type IV and Type V DMF during the assessment for acceptance for filing at OGD.**
- **No duplication of submission of confidential safety information to FDA outside of the DMF process so IP protection can be adequately maintained.**
- **Ongoing dialog between industry and FDA to improve and update the information in the IID and make it useable to both industry as well as FDA.**
- **Broad communication to industry from FDA OGD concerning the policies to be used related to ANDA IID references which should be used to prove a precedence of use and use level of a particular excipient for a specific route of administration once these mechanisms (described above) are appropriately worked out.**

What are FDA OGD's Needs?

- IPEC Americas needs to understand what FDA OGD expects from the listings in the IID and how the information in the IID is utilized both at time of filing and during ANDA review.

Substance Registration System (SRS) Nomenclature – Issues & Potential Unintended Consequences when used by OGD during acceptance to file determinations?

Generic listing vs. Specific Grade listing for commonly used excipients – max. precedent levels

- There are many inconsistencies in naming of materials listed in the IID, including but not limited to: 1) use of common names (hydroxypropyl methylcellulose, dimethicone), 2) generic names (hypromelloses, ethylcelluloses, silicone), 3) trade names (Dimethicone MDX4-4210) 4) etc. (refer to Exhibit 1). Some of the listings include various grades and/or mixtures (refer to examples for Cyclomethicone, simethicones, silicone) while others may be more specific (dimethicone 350 & 1000).

- It is interesting to note that whereas the term "cyclomethicone" has been assigned only **one UNII code**….but could include either a single or mixture of different cyclomethicone molecules with significantly different toxicology profiles(refer to table in Exhibit 3), the term "dimethicone" which based on USP NF includes polydimethylsiloxane, trimethylsiloxy-terminated fluids between 20 – 30,000 cSt has been assigned **several different UNII codes** (even though the toxicology profile for all these fluids is very similar because they are non-functional POLYMERS).

Listing of Mixtures

- Since the first of the year, simethicone customers have begun to request the "UNII" code number for the products they purchase. Currently UNII codes have not been assigned to mixtures; however, based on a search of the FDA UNII code LISTING, components of simethicone (e.g. dimethicone and silicon dioxide) sometimes reference that they are components of simethicone, including specific simethicone products such as DOW CORNING Q7-2243 LVA Simethicone (refer to Exhibit 2 table of UNII listings). NOTE: There

are several different "simethicone" products, each potentially being manufactured differently using different viscosities of dimethicone, different types/forms of silica and different additives…..but all meeting the simethicone monograph. None of these various simethicone products are currently differentiated on the IID.

Problems Encountered by Generic Drug & Excipient Manufacturers

- Some Examples of Grade & Mixture Issues:

  - ***Hypromelloses***

    - There are inconsistencies in the naming of hypromellose (alternate compendia name is hydroxypropylmethylcellulose or HPMC) types listed in the IID, both before and after the SRS was implemented. (see Exhibit 5) These were referred to as both "hydroxypropyl methylcellulose" and, e.g. "hydroxypropyl methylcellulose 2906" in the old IID listing.
    - In the new IID listing, the general category for hypromelloses is still listed along with other nomenclature, e.g. "hypromellose 2208 (15000 mPa.s) and hypromellose 2910 (15000 mPa.s).
    - The only types of HPMC (Hypromellose or hydroxypropyl methylcellulose) are 1828, 2208, 2906 and 2910, as defined by methoxy and hydroxpropoxy content in the compendial monographs. There are only 3 viscosity grades each listed for Hypromellose Types 2208 and 2910 yet there are more than 10 viscosity grades manufactured and used in formulations for each of these types.
    - To compound the problem with HPMC listings in the IID, there are separate listings for hydroxypropyl methylcellulose and these are different than those listed under hypromellose. Not all of the hydroxypropyl methylcellulose types are correct either, e.g. there are listings for "hydroxypropyl methylcellulose 100", "hydroxypropyl methylcellulose 603", "hydroxypropyl methylcellulose 2906" and "hydroxypropyl methylcellulose 4000". The problem is that there are no types 100, 603 and 4000, these are likely viscosity grades but include particular commercial product numbers (ie; 603).
    - As seen in the IID searches below, you can see why the industry is confused about what should be referenced for something like Hypromellose 2910(5 MPA s). In the past the generic listing for Hypromelloses (UNII 3NXW29V3WO) and the Maximum Potency of 670.04 mg was used as a reference in ANDAs for all grades of Hypromellose to demonstrate safe levels of use in oral applications. The same safety data covers all grades of Hypromellose so this is appropriate.

Inactive Ingredient Search for Approved Drug Products

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Search Results for: "hypromelloses"

INACTIVE INGREDIENT	ROUTE;DOSAGE FORM	CAS NUMBER	UNII	MAXIMUM POTENCY
HYPROMELLOSES	ORAL; CAPSULE, SUSTAINED ACTION		3NXW29V3WO	670.04MG
HYPROMELLOSES	ORAL; TABLET, COATED		3NXW29V3WO	245.00MG
HYPROMELLOSES	ORAL; TABLET, CONTROLLED RELEASE		3NXW29V3WO	65.70MG
HYPROMELLOSES	ORAL; TABLET, DELAYED ACTION, ENTERIC COATED		3NXW29V3WO	127.29MG
HYPROMELLOSES	ORAL; TABLET, EXTENDED RELEASE		3NXW29V3WO	400.00MG
HYPROMELLOSES	ORAL; TABLET, FILM COATED		3NXW29V3WO	536.80MG
HYPROMELLOSES	ORAL; TABLET, MULTILAYER, EXTENDED RELEASE		3NXW29V3WO	8.40MG
HYPROMELLOSES	ORAL; TABLET, ORALLY DISINTEGRATING		3NXW29V3WO	6.11MG

Inactive Ingredient Search for Approved Drug Products

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Search Results for: Hydroxypropyl Methylcellulose E5

INACTIVE INGREDIENT	ROUTE;DOSAGE FORM	CAS NUMBER	UNII	MAXIMUM POTENCY
HYDROXYPROPYL METHYLCELLULOSE E5	ORAL; CAPSULE			9.00MG
HYDROXYPROPYL METHYLCELLULOSE E5	ORAL; TABLET		Pending	1.50MG

Inactive Ingredient Search for Approved Drug Products

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Search Results for: "hypromellose 2910

INACTIVE INGREDIENT	ROUTE;DOSAGE FORM	CAS NUMBER	UNII	MAXIMUM POTENCY
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL; TABLET, SUSTAINED ACTION, COATED			6.00MG
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL; TABLET, SUSTAINED ACTION, FILM COATED			54.00MG
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL-21; TABLET			0.75MG
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL-28; TABLET			0.75MG
HYPROMELLOSE 2910 (5 MPA.S)	ORAL; TABLET			2.02MG
HYPROMELLOSE 2910 (6 MPA.S)				1.76MG
HYPROMELLOSE 2910 (6 MPA.S)				6.43MG

If the new SRS nomenclature is used to determine the acceptable level of Hypromellose 2910 (5 MPA s), this would result in saying that levels over 2.02 mg/dose might require full safety data which doesn't make any sense!

- The UNII code references in the IID are very confusing to customers. Cellulose ethers are manufactured and sold according to viscosity grades. Most of these grades do not have UNII numbers but since the SRS was implemented many customers are asking for the UNII codes. These were rarely requested by customers prior to the SRS implementation. Many of the CAS numbers are missing in the IID and many of the UNII numbers are listed as "pending". In most cases, one UNII code is assigned to a single nominal viscosity grade, however, for Hypromellose 2208 (80000 – 120000 mPa.s)) there is also one UNII code assigned. It is unclear if this is a single grade with a 40000 mPa.s viscosity range or a range of nomial viscosity grades.

- ***Other Cellulose Ethers***

  - The same naming issues are evident in listings for ethylcellulose, hydroxypropylcellulose and methylcellulose. (see Exhibit 5)

  - All cellulose ethers are classified by viscosity grade and sometimes other properties, e.g. degree of substitution. There is one UNII code each for all of the Carboxymethylcellulose Sodium and Hydroxypropyl Cellulose IID listings, but there is no mention of any viscosity grades for these polymers in the IID. Hydroxypropylcellulose is listed generically as well as by some viscosity

grades but all have the same UNII codes. Ethylcellulose has different UNII codes for the listed viscosity grades but the same UNII code for the "ethylcelluloses".

- ***Simethicones***

  As shown in Exhibit 1-3, there are various inconsistencies on the current (and historical versions) of the IID list with regards to silicones.

  1. Small "cyclomethicone" molecules, potentially consisting of either a single molecular size or a mixture of sizes (e.g. cyclic with 4 SiO groups, aka D_4, cyclic with 5 SiO groups, aka D_5 and cyclic with 6 SiO group, aka D_6) have been covered under a single UNII code; whereas, it appears that high molecular weight dimethicone polymers have been assigned different UNII codes based on their viscosity. As shown in the information in Exhibit 3, the different "sizes" of Cyclomethicone molecules can have a significant impact on "toxicity"; whereas, changing from a dimethicone viscosity of 20 cSt t0 100,000 cSt has little, if any impact on the "toxicity" of the materials (toxicology summaries and/or studies available from Dow Corning, upon request).
  2. Simethicone is currently listed in the IID database have not been assigned UNII codes because they are mixtures; however, in some cases components of a specific simethicone product have been assigned UNII codes as referenced in the UNII code listing (see Exhibit 2). It should be noted that simethicones are NOT produced by simply blending a dimethicone + silica and there are several DIFFERENT simethicone products produced with different dimethicone viscosities, different sources/types of silica and significantly different manufacturing steps; however, they are all produced to meet the USP monograph for simethicone. Care should be taken in assigning UNII codes to the components of simethicone, and not to the material itself. This would be even more pronounced for silicone emulsions…
  3. Silicone Pressure Sensitive Adhesives (PSAs). There are different types of silicone PSAs….yet it is extremely unclear for the way they are currently listed in the IID database what the actual ingredients are (silicone polyester film strip vs silicone adhesive 4102). Nomenclature/ standardization of these products should be considered. Dow Corning has provided guidance on this in two separate communications to the FDA, a copy of which is available, upon request.
  4. SILICONE…there is a number of listings on the IID list entitled "SILICONE" yet that would be equivalent to having a listing entitled "HYDROCARBON". There are many different types of silicones, some reactive, some inert. There are **silicone** fluids, polymers, single molecules, gums, resins, elastomers, etc. This is a prime example of where an industry expert might be usefull in helping review/suggest how a listing might be improved.

- ***Polyethylene Oxides***

  - In July, 2011 the IID was updated and the term "Polyethylene Oxides" was deleted even though this is the compendial name for this material. The term "Polyethylene Glycol" was used instead but only for two specific grades of the material and the generic term disappeared.
  - Refer to information referenced in Exhibit 4 for additional details on the magnitude of the problems encountered and what supporting information exists to support previous approaches to referencing precedence of use for this material.

- **KEY POINT**: Polyethylene Oxide is a different material than Polyethylene Glycol even though the two materials have the same CAS number. The differences are molecular weight and the manufacturing process. Polyethylene Oxide should not be called Polyethylene Glycol.
- The molecular weight of Polyethylene Oxide begins at 100,000 and goes up to 7,000,000 whereas Polyethylene Glycol only goes up to a molecular weight of 40,000.
- The Polyethylene Oxides have not been consistently named in the IID. The same family of material has been described as Polyethylene Oxide Oral and Polyethylene Oxide 200K Oral and 7000K Oral with various maximum potency limits. All of these materials are the same product with the only difference being molecular weight. The molecular weight difference does not impact toxicity.
- The following list was extracted from the 2010 version of the IID
    - POLYETHYLENE OXIDE~ORAL; TABLET~25322683~3WJQ0SDW1A~57.86~MG
    - POLYETHYLENE OXIDE~ORAL; TABLET, CONTROLLED RELEASE~25322683~3WJQ0SDW1A~252.14~MG
    - POLYETHYLENE OXIDE~ORAL; TABLET, EXTENDED RELEASE~25322683~3WJQ0SDW1A~335.79~MG
    - POLYETHYLENE OXIDE~ORAL; TABLET, SUSTAINED ACTION~25322683~3WJQ0SDW1A~543.90~MG
    - POLYETHYLENE OXIDE~ORAL; TABLET, SUSTAINED ACTION, FILM COATED~25322683~3WJQ0SDW1A~180.00~MG
    - POLYETHYLENE OXIDE 200K~ORAL; TABLET, EXTENDED RELEASE~~Pending~81.43~MG
    - POLYETHYLENE OXIDE 7000K~ORAL; TABLET, EXTENDED RELEASE~~Pending~73.70~MG
- Since the toxicity is not impacted by molecular weights within the range of 100,000 to 7,000,000, and the maximum potency for Polyethylene Oxide in previously published editions of the IID was 543.90 mg for all grades, this should be the maximum potency applicable to all molecular weight grades of Polyethylene Oxide.

Some Excipients dropped from the IID –

- Hydroxypropyl Methylcellulose

  As noted previously, a generic listing for Hydroxypropyl Methylcellulose is no longer present in the new IID. Also, changing nomenclature by adding or deleting viscosity grades has caused conf*usion among users an*d FDA reviewers. Reviewers are citing specific grades and asking for the full toxicology studies on grades not listed even though these grades have been used in approved drugs for decades.

- Ethyl cellulose

  Ethylcellulose used to be listed generically which covered all viscosity grades. The IID now lists "ethylcelluloses" along with one listing each for "ethylcellulose 20 mPa.s and ethylcellulose 50 mPa.s. There are at least 6 other ethylcellulose viscosity grades commonly used, however, customers do not

know how to interpret "ethylcelluloses" and are now reluctant to continue using these other viscosity grades since they are not specifically listed.

- Dimethicone 360

  It appears that in an attempt to clean-up the database the FDA removed a reference to the use of dimethicone being used in approved transdermal drug delivery systems (the item below was on the IID list in 2010, but is no longer listed). This was the only reference to the use of dimethicone fluid on the IID list for TDDS….and we are aware of at least 3 commercial patches in the US that use different viscosities of dimethicone fluid.

~~dimethicone 360~~	~~TRANSDERMAL~~	~~Film, controlled release~~	-	~~Pending~~	~~564~~

- Polyethylene Oxide

  Polyethylene Oxide used to be listed generically under this name which covered all molecular weight grades with a fairly high maximum potency level of 543 mg. The IID now lists only two specific molecular weight grades, 200K and 7000K and changed their name to Polyethylene Glycol. The maximum potency level which is listed for each of these specific grades is much lower than the 543 mg which has been used for all grades for many years. There are eight other pharmaceutical molecular weight grades that are commonly used in approved drug products in the U.S., however, customers do not currently know where to find the listing or how to interpret the IID in its current form for the Polyethylene Oxide products since this compendial nomenclature for the material is no longer listed anywhere in the IID and there is no generic listing which covers the other grades or the higher levels of use. Reviewers are citing specific grades and asking for tox data on grades not listed or for levels of the listed grades which are higher than the low levels which are now listed for that grade.

Impact on ANDAs – Unjustified Delays & Refuse to File Letters

The confusion that currently exists throughout industry regarding what FDA OGD expects regarding IID references for these materials and many others with similar issues is significantly affecting generic drug development since many pharmaceutical companies do not know which excipients they can use in their formulations without having significant regulatory concerns when they file their ANDA. Many excipients that can improve the quality of drug products are sometimes being avoided due to regulatory uncertainty once a pharmaceutical company has been subjected to an unexpected Refuse to File letter from FDA OGD that has caused delays in approval.

FDA OGD has been requesting full safety information from ANDA sponsors for specific grades of many commonly used excipients just because the level used in the ANDA are higher than the level listed for the specific grade specified in the IID using the new SRS nomenclature. This type of safety data does not exist in many cases for specific grades of excipients and data regarding the safety of the whole family of similar

materials has been used to substantiate safe use of these excipients for decades without any known patient safety concerns.

Realities of Existing Safety Data for Common Excipients

Individual Grades vs. Family Data

Many excipients are part of an excipient family of similar products and the different grades that exist have no impact on the safety of the material. In these cases, the use of a generic listing for the excipient family in the IID which lists the highest level of use in a particular route of administration is appropriate to determine precedence of use levels that support the safety of the excipient for a given application of any of the excipients in the family. The examples below emphasize the importance of allowing for the use of generic listings and highest levels when cross-referencing an excipient in the IID for ANDA filings.

Hypromellose and other Cellulosics

- There are many grades (industrial, cosmetic, food and excipient) and viscosities (5 mPa.s, 50 mPa.s, 5000 mPa.s etc) for HPMC as well as all other cellulose ethers. Numerous toxicology studies have been performed on all of these **with consistent results, regardless of the grade tested**. Further, the toxicology of the different types of HPMC is not dependent on the methoxy and hydroxpropoxy content.
- CFSAN in the Federal Register on July 15, 2011 published that viscosity differences in cellulose ethers are not a factor in safety/toxicology when used as food additives. The petitioner did not submit any safety or tox data stating that viscosity is not a safety factor and FDA CFSAN agreed citing FAO/WHO (JECFA) evaluations.

  SUMMARY: The Food and Drug Administration (FDA) is amending the food additive regulations for hydroxypropyl cellulose by lowering the minimum permitted viscosity from 145 centipoises (cPs) to 10 cPs and to permit its use as a binder in dietary supplements. This action is in response to a petition filed by Nisso America, Inc.

  DATES: This rule is effective July 15, 2011. Submit either electronic or written objections and requests for a hearing by August 15, 2011.
- Manufacturers are frequently asked to provide toxicology information to customers either in preparation for a FDA submission or in response to a Refuse to File or deficiency letter received when they want to use an excipient in an amount higher than listed in the IID. What is a significant increase in use level – 0.5 mg, 5 mg or 500 mg - if the NOAEL is 5 times higher than the highest listing in the IID?
- Since the implementation of the SRS, we have also seen a significant increase in requests from customers who are getting deficiency or refuse to file letters from FDA or are proactively asking for toxicology studies specific to the viscosity grade being used in the formulation. These materials have been studied extensively and many are compendial excipients that have been used in pharmaceuticals, foods and cosmetics for over 50 years without any issues. Their safety and toxicity has been established, published and used by scientific panels and organizations such as JEFCA, EFSA, CIR etc. The toxicology studies were conducted for many different reasons, not solely for use in pharmaceuticals, and were based on the chemistry of the material, not physical properties, and samples representative of the entire product family, not every viscosity grade. Additional studies based on viscosity grades are difficult to

justify from a scientific basis. Industry does not intend to do any further safety studies on these materials unless there is some type of evidence which indicates some type of safety problem.

- Manufacturers who have Type IV DMFs on file for their excipients have included detailed toxicology studies in these DMFs. Customers have stated that FDA has refused to reference the toxicology studies in the DMFs and that they expect excipient companies to provide these studies directly to customers so that they can send in a response to the deficiency letters or to include with their submissions. The level of detail in these studies is considered confidential which is why they have been included in the DMF and have not been provided directly to customers. Frequently, a less detailed summary of the tox studies is made available to customers, however, these have not been sufficient to satisfy these requests from FDA recently. If the detailed study information is already in the excipient company's DMF located at FDA there should be no reason why FDA OGD could not reference this information rather than asking the sponsor to get this information to them outside of the DMF system where confidentiality is fully protected. In most cases, excipient manufacturers do not intend to re-submit this type of information to FDA outside of the DMF system or provide this level of confidential information to their customers. Summary information should be adequate for the review at the time of filing along with a reference to a DMF where the actual reviewer can obtain the detailed information if needed.

Dimethicones

- Currently there are many grades (industrial, cosmetic, topical excipient and parenteral) and viscosities (20 cSt, 100 cSt, 350 cSt, 1000 cSt, 12500 cSt, etc) for dimethicone. Numerous toxicology studies have been performed on all of these fluids (industrial through parenteral) **with consistent results, regardless of the grade tested**. However, to minimize the risk for contamination due to processing and/or packaging (environment, lubricants, employees, etc), it is important to put "GMP" procedures in place when manufacturing materials intended for use in drug products. Refer to Cosmetic Ingredient Review (CIR) Expert Panel Final Report on the Safety Assessment of Dimethicones, published in the international Journal of Toxicology, 22 (Suppl 2): 11-35, 2003.

Polyethylene Oxides

- These materials are very high molecular weight excipients that have very little absorption. The studies which have been performed on both the lower molecular weights and the higher molecular weights show that the safety data for these grades can be applied to the entire family of polyethylene oxide grades. This information has been included in a DMF for Polyethylene Oxide which was filed in 1963 and it has been referenced in many drug products. There is no need to have specific safety data on each grade of Polyethylene Oxide and therefore the highest level of any of the grades which has been used in a given route of administration should be the level used to support the safe use of any of the grades. See Exhibit 4 for a more detailed description to support this approach.

Use of appropriate Risk Management Concepts

ICH published the Q9 guideline on Risk Management and FDA has adopted this guideline as FDA guidance. High level FDA management people including Commissioner Hamburg and CDER's Janet Woodcock have strongly stated that FDA plans to expand their use of appropriate risk management techniques to help FDA streamline the review process and FDA's inspectional capabilities to make sure that FDA is focusing on real

risks and not spending time on minor issues that are low risk to patients. This has also been a point of discussion during Congressional hearings and talks about GDUFA. FDA needs to make the most of it's limited resources and so does industry.

The manner in which FDA OGD is interpreting how to use the IID listings and Maximum Potency levels for evaluating the safety of excipients when referenced in ANDA filings does not appear to be consistent with these comments from FDA management since significant resources both within the FDA as well as in industry are being expended to collect, submit and re-review old safety data on commonly used excipients which have been safely used for years in drugs and as food additives where their levels of use are many times greater than the use in drugs. The risks for using these materials is very low and does not warrant this type of re-review just because the SRS nomenclature now allows for a more detailed listing of individual grades in the IID that does not take into consideration the actual history of use.

IPEC Americas would like to understand how FDA OGD justifies the current policy regarding the IID references from an ICH Q9 Risk Management perspective. IPEC Americas also would like to understand from FDA management how this policy is consistent with the comments made by Commissioner Hamburg and Janet Woodcock regarding the use of ICH Q9 concepts within the agency to focus FDA's resources on higher risk activities. It is hard to understand how FDA OGD can justify having a reviewer spend significant time to read detailed toxicology reports from the 1950s about the safety of Hypromelloses and other Cellulosics when they could be focused on higher risks and lowering the ANDA backlog. IPEC Americas would like ICH Q9 concepts to drive how the IID references are looked at during the ANDA acceptance for filing process and application review stages of drug approval.

Lack of Communication from OGD to the Industry regarding change in approach to grade specific precedent references and certain types of mixtures

The need for a communication to Industry from OGD about use of SRS and UNII in the IID

FDA OGD has not developed any specific guidance documents or sent out any formal notification to industry indicating that they have changed information contained in the IID along with their position on what IID references should be used in ANDA submissions. FDA OGD cannot expect that industry will simply know how they will interpret this now and change the way they develop their products and ANDAs.

A change such as this which can result in Refuse to File and deficiency letters to the ANDA sponsor must be clearly communicated to the industry and a transitional period should be provided for industry to comment on the policy and to switchover to those practices that make sense.

There could be legal implications of the way this practice has developed that should be considered as a more formalized policy is developed. IPEC Americas hopes that a mutually acceptable outcome can be achieved which will resolve the current issues.

Legal status of the IID, and FDA communications of changes to the IID

- The Food, Drug, and Cosmetic Act, and FDA regulations promulgated under the authority of the Act provide the requirements for the use of inactive pharmaceutical ingredients.
- For ANDAs, the regulation describing the requirements (with exception) for inactive ingredients is found at 21 CFR 314.94(a)(9)(ii). That section states "*an applicant shall identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety or efficacy of the proposed drug product.*"
- FDA has chosen to enact this section through reliance on previous drug approvals for various inactive ingredients, dosage forms, and routes of administration. This is accomplished through reference to appropriate listings and potency ranges in the IID.
- FDA had established a long precedence of use for certain IID practices with regards to grades of excipients, mixtures, etc… IID listings of excipients under generic family names and their corresponding maximum potency range (limit) have been used for years to cover all grades of that excipient in the family of similar materials (ie: Hypromelloses, Ethylcelluloses, Polyethylene Oxides, Simethicone etc.)
- Industry has long relied on those practices in developing formulations for generic pharmaceuticals.
- Although the IID is not a creation of regulation, through long use and industry reliance, it has the practical effect of binding FDA action in the same way as a regulation. FDA cannot significantly change IID practices without going through notice and comment rulemaking. This view has been upheld by courts, which have found that where industry significantly relies on an agency's advice and practice, that "regulatory common law" can only be changed through rulemaking. See Alaska Professional Hunters Association, Inc. v. Federal Aviation Administration, 177 F.3d 1030 (DC Cir. 1999).

Potential Legal and Confidentiality Concerns

DMF Implications

- The DMF system was created by FDA regulation to permit a drug applicant (NDA, ANDA, etc…) to incorporate the information contained within the DMF by reference into its application. It is very important to excipient manufacturers that some of their confidential manufacturing information be kept in their DMF and not be made available to their customers for competitive reasons. It is not acceptable to have to re-submit this type of information to FDA directly a second time just so the initial OGD personnel will not have to review the DMF. This type of submission is redundant and would require submission outside of the confidentiality protections offered by the DMF system.
- FDA has not, by regulation or formal guidance document, placed any limitations on when DMF information can be incorporated by reference. For legal/regulatory purposes, the DMF information is part of the NDA/ANDA, and must be reviewed as such at any stage including the determination of acceptance for filing when information from the DMF is required for this determination.
- There is no legal basis for FDA to refuse to file an ANDA on the grounds that necessary information is in the DMF, and not in the physical application.
- If FDA wishes to change its approach from that mandated by regulation, it must promulgate new regulations through notice and comment rulemaking.

Impact of ANDA Delays

- Delays the marketing of generic drugs. This can dramatically increase healthcare costs, particularly if the delay is for a new generic for a "blockbuster" single source pioneer drug. In such situations, the increased healthcare costs to the public can amount to several million dollars per day.
- Delays also Increases the expense of bringing generic drugs to market - reduces incentives for generic drug manufacturers, and limits competition. Again, any delay in bringing these generic drugs to market will result in increasing healthcare costs.
- May result in loss of valuable "first-to-file" status for first generic versions of pioneer drugs.
- FTF status is granted to the first ANDA applicant to submit a substantially complete (eg accepted for filing) ANDA for a particular NDA drug, and any other ANDA applicant that files on the same day.
- Provides a 180-day exclusivity period against other generic approvals for the same drug.
- FTF status is a strong incentive for generic companies to submit ANDAs for new generic drugs, and is necessary because of the risk of lawsuits from pioneer drug companies against early entrants into a particular generic market.
- A refuse to file letter may result in the loss of FTF status and the possible loss of millions of dollars in revenue for a generic drug company.
- The increased risk of a refuse to file letter because of IID issues will create a disincentive for filing ANDAs.

Other IID Issues Creating Confusion –

FD&C Yellow #5 Aluminum Lake

Some customers have received Refuse to File letters from FDA OGD for ANDA products that were formulated with FD&C Yellow #5 Aluminum Lake. They were told by FDA OGD that it was unacceptable to use this colorant and that they should reformulate their product with a different colorant. This is not consistent with current regulation. This colorant is approved for use in any type of drug product as long as the specific requirements in 21 CFR are followed.

In 21 CFR 74.1505, 82.51 and 82.705, the regulations clearly state that “FD&C Yellow #5 (and associated lakes) may be safely used for coloring drugs generally, including drugs intended for use in the area of the eye, in amounts consistent with current good manufacturing practice.”

There is a restriction in 21 CFR 74.1505 for prescription drugs which states that the labels for these products must bear the following warning statement: “This product contains FD&C Yellow #5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow #5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity”.

As long as this warning statement is listed on the labels, we do not understand why FDA OGD would tell an ANDA Sponsor that they could not use this colorant.

FD&C Yellow #5 Aluminum Lake is also listed in the IID as in the following table. However, these maximum potency levels would appear to be over-ridden by the 21 CFR regulations that allow for "amounts consistent with cGMP" to be used for coloring drugs generally.

Search Results for: "FD&C YELLOW NO. 5--ALUMINUM LAKE"

INACTIVE INGREDIENT	ROUTE;DOSAGE FORM	CAS NUMBER	UNII	MAXIMUM POTENCY
FD&C YELLOW NO. 5--ALUMINUM LAKE	ORAL; CAPSULE	12227699	Multiple	0.09MG
FD&C YELLOW NO. 5--ALUMINUM LAKE	ORAL; TABLET	12227699	Multiple	2.423MG
FD&C YELLOW NO. 5--ALUMINUM LAKE	ORAL; TABLET (IMMED./COMP. RELEASE), UNCOATED, CHEWABLE	12227699	Multiple	1MG
FD&C YELLOW NO. 5--ALUMINUM LAKE	ORAL; TABLET, COATED	12227699	Multiple	0.135MG
FD&C YELLOW NO. 5--ALUMINUM LAKE	ORAL; TABLET, FILM COATED	12227699	Multiple	0.6MG
FD&C YELLOW NO. 5--ALUMINUM LAKE	ORAL; TABLET, SUSTAINED ACTION	12227699	Multiple	
FD&C YELLOW NO. 5--ALUMINUM LAKE	ORAL-21; TABLET	12227699	Multiple	0.1MG
FD&C YELLOW NO. 5--ALUMINUM LAKE	SUBLINGUAL; TABLET	12227699	Multiple	0.03MG

What justification does FDA OGD have for telling ANDA Sponsors that they cannot use FD&C Yellow #5 Aluminum Lake when, in fact, these are legal colors allowed for use at cGMP levels with no listed limit?

There has been some controversy in the media over the last few years about some of the azo dyes such as FD&C Yellow #5 possibly causing child hyperactivity. However, as was determined in an FDA Food Advisory Committee hearing on March 30-31, 2011, there is not sufficient data to indicate a causal effect between these colors and child hyperactivity. The FDA Food Advisory Committee determined that no action should be taken on these colors and that current regulation provides appropriate controls for the continued use of these colors in foods, drugs and cosmetics. Therefore, this issue should also not concern FDA OGD.

IPEC would like to understand how a generic drug company is supposed to know that they won't be allowed to use this colorant when it is listed in the IID and allowed by law to be used in any type of drug product provided that the appropriate warning statement is listed on the labels if the product is a prescription drug.

FD&C Red #3 Aluminum Lake

The use of FD&C Red # 3 Aluminum Lake in drug products was delisted during the 1990s and this colorant is no longer listed in 21 CFR as an approved lake for these applications in the U.S. However, the following listings are still included in the IID which has created some confusion regarding the acceptability of this colorant for drug use, especially by companies located in countries where FD&C Red # 3 (Erythrosine)Aluminum Lake is an approved color for use in drugs. Why are the following listings still included in the IID for a delisted color

without any notation about the fact that they were delisted and cannot be used in drug applications? This situation should be cleaned up so as not to create additional confusion going forward.

Search Results for: "FD&C RED NO. 3--ALUMINUM LAKE"

INACTIVE INGREDIENT	ROUTE;DOSAGE FORM	CAS NUMBER	UNII	MAXIMUM POTENCY
FD&C RED NO. 3--ALUMINUM LAKE	ORAL; CAPSULE, SUSTAINED ACTION		Multiple	0.29MG
FD&C RED NO. 3--ALUMINUM LAKE	ORAL; GRANULE		Multiple	50MG
FD&C RED NO. 3--ALUMINUM LAKE	ORAL; POWDER, FOR SUSPENSION		Multiple	0.03%
FD&C RED NO. 3--ALUMINUM LAKE	ORAL; TABLET		Multiple	8MG
FD&C RED NO. 3--ALUMINUM LAKE	ORAL; TABLET (IMMED./COMP. RELEASE), UNCOATED, CHEWABLE		Multiple	4.25MG
FD&C RED NO. 3--ALUMINUM LAKE	ORAL; TABLET, COATED		Multiple	0.541MG
FD&C RED NO. 3--ALUMINUM LAKE	ORAL; TABLET, FILM COATED		Multiple	
FD&C RED NO. 3--ALUMINUM LAKE	ORAL; TABLET, SUSTAINED ACTION		Multiple	0.161MG
FD&C RED NO. 3--ALUMINUM LAKE	SUBLINGUAL; TABLET		Multiple	0.01MG
FD&C RED NO. 3--ALUMINUM LAKE	TOPICAL; SOLUTION		Multiple	0.006%

Need for transitional process to minimize ANDA acceptance for filing issues -

The generic drug and the excipient industry has been significantly impacted by the current FDA OGD policy changes regarding the use of the SRS grade specific nomenclature and maximum potency limits. These policy changes were not adequately communicated to the industry so that a reasonable transition could take place. This has resulted in a significant increase in the issuance of Refuse to File letters and Deficiency Letters to ANDA Sponsors for reasons that do not seem to be science and risk based.

IPEC Americas requests that FDA OGD work collaboratively with industry to develop a transitional process for changing what precedence references will be considered to be acceptable in ANDA submissions to provide assurances that an excipient is safe for an intended use.

IPEC Americas requests that FDA OGD immediately go back to accepting the same type of generic IID references and maximum potency levels that have been considered acceptable for many years. This is needed to reduce the current confusion that exists in the industry concerning the IID and to minimize

unnecessary delays in ANDA review during the transitional period needed to rectify the issues regarding how the current IID is structured and is being used by FDA OGD.

A formalized process needs to be established that includes public input on future deletions, consolidations and modifications of existing information in the IID **prior** to revision.

IPEC Americas also recommends that FDA download the entire IID database into a text file or spreadsheet form **BEFORE** making any quarterly updates and post these versions of the IID on the FDA website for public access along with the date of the download. Each quarterly update would then have a record of what was there before the update and this could be utilized during discussions with reviewers on appropriate excipient precedences for use in ANDAs. These quarterly downloads should be publically accessible on the FDA website for approximately three years if possible. This would facilitate less confusion when changes are made which could result in certain references disappearing from the IID or changing in a significant manner that could impact ANDA submissions.

IPEC Americas also requests that a **one to two year transition period** be established before implementation of any new policies regarding changes in the types of references considered to be appropriate for supporting the use of an excipient in an ANDA and the need to supply additional safety data.

IPEC Americas is willing to help establish a team of industry experts who can meet with FDA as appropriate and act as subject matter experts during this transitional period so that appropriate policies and procedures can be developed that will work adequately for FDA and for the industry.

Once these policies and procedures are developed collaboratively with industry, IPEC Americas requests that FDA OGD incorporate these approaches in a formal guidance or Q&A document that could be posted on the FDA website to inform the industry on what is expected. Developing this type of guidance or Q&A document would also help provide the appropriate public notification needed and the mechanism for public comments about the proposals. This will be critical to be done before changes in policy are implemented on something as important as this.

Mechanisms for providing appropriate information to support historical IID levels which have been used in the past –

IPEC Americas realizes that FDA may need to have additional data on some excipients to justify that the safety data that exists can be used to cover the safety of a family of similar excipients. However, there needs to be a better way to share this information than simply requesting it over and over again with each ANDA which may have a different grade of an excipient that belongs to a family of excipients covered by the same safety data. This approach is redundant and wastes precious resources both at the FDA and within industry.

A mechanism needs to be developed which allows the excipient industry to supply supportive safety information, data and appropriate bridging arguments on an excipient or a given family of excipients **on a one-time basis** directly to FDA so that the previous precedence of use limits can be utilized going forward where

justified by the data. This could be done during the transition period and would require a proactive review of this safety information by FDA outside of a submitted ANDA.

Since the safety assessment of most of these excipient families is pretty straight-forward, this mechanism should **not require a full re-review of all the detailed toxicology study reports** in most cases but instead should involve a simple review of various toxicology summary reports, bridging arguments and qualified expert conclusions.

IPEC Americas recommends that FDA notify the entire industry using the Federal Register or other official forum that they are willing to perform proactive safety reviews during the fixed transitional period which gets established and that this would represent a one-time-opportunity to provide safety information outside of an ANDA review to try to justify why the original maximum exposure levels that were listed for the generic listings should be used for all the grades of an excipient. This would then put the burden of bringing this information forward on the excipient companies who may have this kind of information available. If they react and work with FDA on their excipients they would then be able to gain acceptance of the higher limits listed for the generic listings and use this information for all the grades in the family. The outcome would need to be documented in the literature so this type of assessment will not be needed again in the future.

As mentioned above, IPEC Americas is willing to help establish a team of industry experts who can meet with FDA as appropriate and act as subject matter experts during the transitional period so that appropriate policies and procedures regarding the level of safety assessment that is needed in these situations can be developed that will work adequately for FDA and for the industry.

Ongoing Dialog –

IPEC Americas is interested in having an on-going dialog with FDA on excipient IID related issues so that the IID can be improved and updated periodically to include appropriate nomenclature and maximum potency levels for excipients and excipient families. IPEC Americas realizes that this may be a complex process, especially during the transition period, and is ready to provide access to industry experts who can assist in the improvement process. Therefore, IPEC Americas see this initial meeting on this topic as hopefully only a first step to a continuous process which can provide assurance to FDA OGD and to industry that the information in the IID and the policies and procedures on how to use this information is appropriate and fully understood by both industry and regulators.

IPEC Americas appreciates this opportunity to discuss our concerns with the IID and the practices used by FDA OGD regarding the use of IID listings to establish a precedence of use reference for ANDA filings. Hopefully, the information presented in this Backgrounder document and what will be presented during the meeting on December 9th will be useful to FDA OGD as you re-assess the policies related to these issues and establish science and risk based approaches going forward.

EXHIBIT 1

Inconsistencies and issues with the current use of UNII numbers in the IID list

Inactive Ingredient	Route;	dosage form	CAS#	UNII	Max Potency
CYCLOMETHICONES - different size cyclic molecules, e.g. $(Me_2SiO)_4$, $(Me_2SiO)_5$,; $(Me_2SiO)_6$,; $(Me_2SiO)_{6+}$, and mixtures of molecules….with different associated tox profiles, yet they all been assigned the same UNII code (also all meet the current Cyclomethicone monograph)					
cyclomethicone	ORAL	Powder for solution		NMQ347994Z	
cyclomethicone	TOPICAL	Cream augmented		NMQ347994Z	7.6 %
cyclomethicone	TOPICAL	Emulsion aerosol foam		NMQ347994Z	5.3 %
cyclomethicone	TOPICAL	Emulsion, cream		NMQ347994Z	13 %
cyclomethicone	TOPICAL	Lotion		NMQ347994Z	4 %
DIMETHICONE – different viscosity "family" of polymers; however, above a certain viscosity they all have the SAME tox profile and are all referenced in the same USP monograph…. Yet these fluids are assigned different UNII codes In addition, the one listing for TDDS was removed from the IIG list without a trace…yet different viscosity dimethicones (e.g. 100, 350 and 1000) have all been used in approved TDDS products, some for more than two decades!					
~~dimethicone 360~~	~~TRANSDERMAL~~	~~Film, controlled release~~	-	~~Pending~~	~~564~~
dimethicone 1000	ORAL	Capsule, enteric coated pellets	9006659	Pending	2.5 mg
dimethicone 350	ORAL	Capsule	9006659	2Y53S6ATLU	3.7 mg
dimethicone 350	ORAL	Capsule, sustained action	9006659	2Y53S6ATLU	0.1 mg
dimethicone 350	TOPICAL	Emulsion, cream	9006659	2Y53S6ATLU	1 %
dimethicone 350	TOPICAL	Solution	9006659	2Y53S6ATLU	0.5 %
SIMETHICONES – currently UNII codes have not been assigned to mixtures; however, based on a search of the UNII code nomenclature, components of these products have been listed and referenced separately as dimethicone and silicon. There are several different "simethicone" products, each potentially being manufactured differently using different viscosities of dimethicone, different types/forms of silica and different additives…..but all meeting the simethicone monograph….					
simethicone	ORAL	Powder, for oral suspension	8050815	Multiple	18.9 %
SIMETHICONE EMULSIONS – currently UNII codes have not been assigned to mixtures; however, see comments above for simethicones….same analogy applies AND, the various simethicone emulsion products available are probably MORE variable (process, dimethicone visc, type/source silica, additives, etc) than even the simethicone products.					
simethicone emulsion	ORAL	Capsule, sustained action		Multiple	15.63 mg
SILICONE EMULSION – currently the IIG shows that UNII codes are not applicable to silicone emulsions, yet the only difference between silicone emulsion and simethicone emulsion is that the main ingredients in silicone emulsion are dimethicone, silica and water and the main ingredient in silicone emulsion are dimethicone and water (no silica).					
Silicone EMULSION	ORAL	Capsule, sustained action		N/A	0.078 mg

EXHIBIT 1 (cont.)

Inactive Ingredient	Route;	dosage form	CAS#	UNII	Max Potency
SILICONE PRESSURE SENSITIVE ADHESIVES (PSAs) – silicone PSAs are currently used in various transdermal systems. There are basically two different FAMILIES of these adhesives (standard or 7-440X, 7-450X, 7-460X and amine compatible, 7-410X, 7-420X and 7-430X), each including "customized" formulations/processing…..but it is NOT always clear from the current IID listing what family of silicone adhesive is listed (except in the case of 4102 and 4502). Whereas some of them have UNII numbers pending, others have an "N/A" in the UNII column.					
Dimethicone MDX4-4210	TRANSDERMAL	Film, controlled release		Pending	
silicone/POLYESTER FILM STRIP	TRANSDERMAL	Film, controlled release		N/A	873 mg
silicone/POLYESTER FILM STRIP	TRANSDERMAL	Patch		N/A	485.2 mg
silicone/POLYESTER FILM STRIP	TRANSDERMAL	Patch, controlled release		N/A	10.91 mg
silicone ADHESIVE 4102	PERCUTANEOUS	Patch, controlled release		Pending	165 **cms**
silicone ADHESIVE 4102	TRANSDERMAL	Film, controlled release		Pending	228.23 mg
silicone ADHESIVE 4502	TRANSDERMAL	Film, controlled release		Pending	57.14 mg
SILICONE – silicone is a GENERIC term generally used to describe any number of polymeric materials containing silicon, carbon, hydrogen, oxygen and sometimes other chemical elements. Seldom is the term silicone used to describe a specific chemical molecule or compound…yet the term "silicone" is listed in the IID (and the UNII column shows that numbers are pending). It is my belief that the term "silicone" referred to below include such forms as: silica, polydimethyl siloxane fluids, gums and elastomers (probably both functional and non-functional)					
silicone	IM - IV	Injection		Pending	
silicone	INTRAUTERINE	Suppository, insert, controlled release		Pending	60 mg
silicone	ORAL	Capsule		Pending	15 mg
silicone	ORAL	Capsule, hard gelatin		Pending	0.42 mg
silicone	ORAL	Capsule, sustained action		Pending	0.14 mg
silicone	ORAL	Powder, for suspension		Pending	0.1 %
silicone	ORAL	Suspension		Pending	
silicone	ORAL	Tablet		Pending	
silicone	TOPICAL	Shampoo, suspension		Pending	
silicone	TRANSDERMAL	Film, controlled release		Pending	353.51 mg
silicone	VAGINAL	Drug delivery system		Pending	8.7 mg
silicone	VAGINAL	Intrauterine device		Pending	27.48 mg

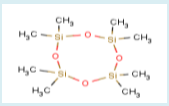
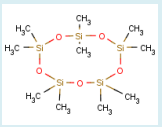
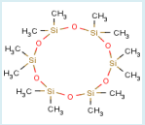
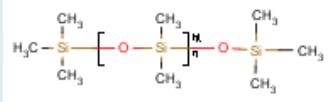
EXHIBIT 2

Taken from the FDA UNII database

Preferred Substance Name	UNII	Substance Name	Molecular Formula
DIMETHICONE	92RU3N3Y1O	Dimethicone component of simethicone	C4H12Si(C2H6OSi)n
DIMETHICONE 410	TYU5GP6XGE	Component of DOW CORNING Q7-2243 LVA Simethicone	C4H12Si(C2H6OSi)n
SILICON DIOXIDE	ETJ7Z6XBU4	Silicon dioxide component of simethicone	2O.Si

EXHIBIT 3

Toxicity information from US National Library of Medicine

Organism	Test Type	Route	Reported Dose (Normalized Dose)	Effect	Source
Octamethylcyclotetrasiloxane, aka D_4				**RN: 556-67-2**	
rabbit	LD50	skin	794uL/kg (0.794mL/kg)	KIDNEY, URETER, AND BLADDER: HEMATURIA	National Technical Information Service. Vol. OTS0538262,
rat	LC50	inhalation	36gm/m3/4H (36000mg/m3)	• BEHAVIORAL: EXCITEMENT • LUNGS, THORAX, OR RESPIRATION: DYSPNEA • SKIN AND APPENDAGES (SKIN): HAIR: OTHER	National Technical Information Service. Vol. OTS0557551,
rat	LD50	oral	1540mg/kg (1540mg/kg)	BEHAVIORAL: TREMOR	National Technical Information Service. Vol. OTS0538262,
rat	LD50	skin	1770mg/kg (1770mg/kg)	• BEHAVIORAL: TREMOR • GASTROINTESTINAL: CHANGES IN STRUCTURE OR FUNCTION OF SALIVARY GLANDS • LIVER: OTHER CHANGES	National Technical Information Service. Vol. OTS05382
Decamethylcyclopentasiloxane, aka D_5				**RN: 541-02-6**	
rabbit	LD50	skin	> 16mL/kg (16mL/kg)		Toxicology and Applied Pharmacology. Vol. 28, Pg. 313, 1974. Link to PubMed
rat	LC	inhalation	> 2700mg/m3/4H (2700mg/m3)		National Technical Information Service. Vol. OTS0572802,
rat	LD50	oral	> 24134mg/kg (24134mg/kg)		National Technical Information Service. Vol. OTS0572801,
Dodecamethylcyclohexasiloxane, aka D_6				**RN: 540-97-6**	
rat	LD50	oral	> 50gm/kg (50000mg/kg)	• BEHAVIORAL: SOMNOLENCE (GENERAL DEPRESSED ACTIVITY) • LUNGS, THORAX, OR RESPIRATION: RESPIRATORY STIMULATION • LUNGS, THORAX, OR RESPIRATION: OTHER CHANGES	National Technical Information Service. Vol. OTS0572798
Dimethicone				**RN:9006-65-9**	

Organism	Test Type	Route	Reported Dose (Normalized Dose)	Effect	Source
rat	LD50	oral	> 50gm/kg (50000mg/kg)	• > 20gm/kg (20000mg/kg)	Gekkan Yakuji. Pharmaceuticals Monthly. Vol. 9, Pg. 759, 1967

EXHIBIT 4

POLYETHYLENE OXIDE (POLYOX™) versus PEG – The Need for Differentiation in Nomenclature and use of appropriate Potency Ranges for All Grades

One of the most frequent questions encountered from customers when discussing polyethylene oxide (POLYOX™) grades is – how is this product different from polyethylene glycol (PEG)? The standard answer consists of 4 basic elements: 1) the physical state of this product, 2) the molecular weight differences, 3) the process to make such products, and 4) the different impurity profiles. There are also some differences in how these two products are used in pharmaceuticals, along with the overall toxicity information surrounding both. All of these elements solidify the need to have a distinction between the two products in the FDA's IID list. The compendial nomenclature for POLYOX™ is Polyethylene Oxide and that is how it should be listed in the Inactive Ingredient Database (IID) so it is not confused with Polyethylene Glycol (PEG) which is a significantly different material.

The most obvious difference when you look at the POLYOX™ and PEG product lines is the actual product in itself. All the POLYOX™ grades are powders, and they all have a melting point close to 65°C. The PEG products look different, as they have some grades (higher in molecular weight) that are powders, but they also have grades that are liquids. Figure 1 below provides more insight on the influence of product molecular weight on its melting temperature. PEG products also come in powder, granular, and flake grades. POLYOX™ does not have such different particle size differences between grades, and any grades that have different particle size distribution are simply sieved to achieve the desired range.

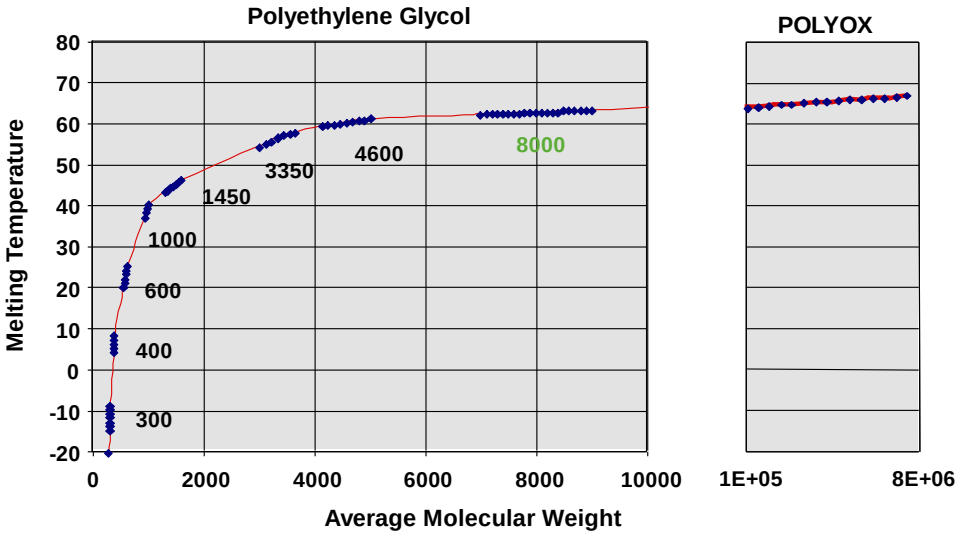


Figure 1: Effect of molecular weight on polyethylene glycol melting temperature

The molecular weight of the PEG and POLYOX™ product lines are significantly different. PEG products are available up to 40,000 in molecular weight, whereas POLYOX™ begins at 100,000 and increases all the way to 9,000,000 in some industrial grades. So, although the chemical structures of the two products appear to be

similar, represented with the same polymeric repeating units, the lengths of these polymers are quite different. Table 1 shows the pharmaceutically-approved PEG and POLYOX™ grades that are available through the Dow Chemical Company.

Dow Chemical Product	Average Molecular Weight	Supplied Form
CARBOWAX™ SENTRY™ PEG 300 NF	300	Liquid
CARBOWAX™ SENTRY™ PEG 400 NF	400	Liquid
CARBOWAX™ SENTRY™ PEG 600 NF	600	Liquid
CARBOWAX™ SENTRY™ PEG 1000 NF	1,000	Fused solid (waxy)
CARBOWAX™ SENTRY™ PEG 1450 NF	1,450	Flake, Molten
CARBOWAX™ SENTRY™ PEG 3350 NF	3,350	Granular, Powder, Flake, Molten
CARBOWAX™ SENTRY™ PEG 4000 NF	4,000	Granular, Powder, Flake, Molten
CARBOWAX™ SENTRY™ PEG 4600 NF	4,600	Granular, Molten
CARBOWAX™ SENTRY™ PEG 8000 NF	8,000	Granular, Powder, Molten
POLYOX™ WSR N-10 NF	100,000	Free-flowing powder
POLYOX™ WSR N-80 NF	200,000	Free-flowing powder
POLYOX™ WSR N-750 NF	300,000	Free-flowing powder
POLYOX™ WSR 205 NF	600,000	Free-flowing powder
POLYOX™ WSR 1105 NF	900,000	Free-flowing powder
POLYOX™ N-12K NF	1,000,000	Free-flowing powder
POLYOX™ N-60K NF	2,000,000	Free-flowing powder
POLYOX™ WSR 301 NF	4,000,000	Free-flowing powder
POLYOX™ WSR COAG NF	5,000,000	Free-flowing powder
POLYOX™ WSR 303 NF	7,000,000	Free-flowing powder

Table 1: Pharmaceutically-approved PEG and POLYOX™ grades that are available through Dow Chemical

To achieve such differences in polymeric chain lengths requires different chemical processes. Figure 2 below shows how the two chemical reactions vary, and such differences in chemistry also require different manufacturing processes.

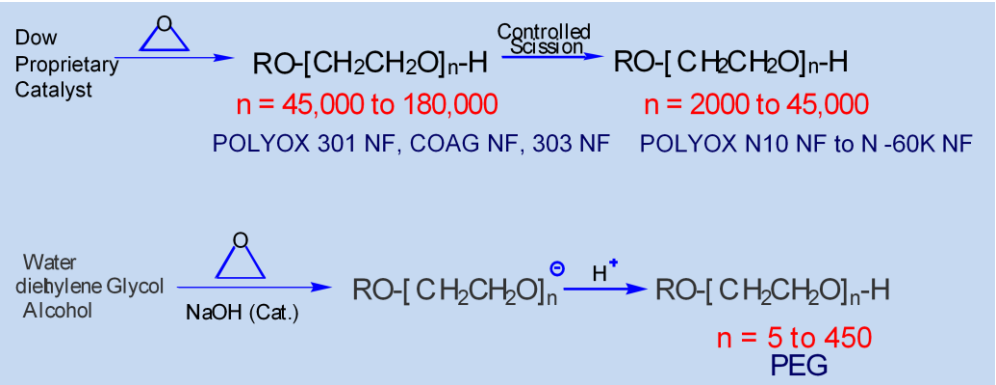


Figure 2: Chemistries required in making PEG and POLYOX™ grades

The process to make POLYOX™ begins with a proprietary calcium-based catalyst that is reacted with ethylene oxide. Fumed silica is added as a flow aid. After the reaction, the resulting product will be extremely high in molecular weight. If a particular batch is scheduled to be one of our higher grades, the product is simply packaged off in polyethylene-lined fiber drums. If a batch is scheduled to be either a mid or low molecular weight grade, then the material undergoes an extra step, where a controlled molecular chain scission takes place via irradiation to achieve the desired product grade. Butylated hydroxytoluene (BHT) is added to POLYOX™ as an antioxidant to help minimize the oxidative degradation that naturally occurs in this product.

The process to make a PEG is quite different. Diethylene glycol is first catalyzed with a suitable hydroxide and then reacted with ethylene oxide. The amount of diethylene glycol and ethylene oxide determine the molecular weight. Low molecular weight polyethylene glycol products (molecular weight 200 to 1000) will be in a liquid to waxy semi-solid state at room temperature and are often packaged in drums. Higher molecular weight PEG products are manufactured from either diethylene glycol or a low molecular weight PEG. Either initiator is reacted with hydroxide catalyst and ethylene oxide, resulting in a product that forms a waxy solid at room temperature. This high molecular weight is available in multiple forms (molten, powder, granular or flake) produced via different additional processing steps. Solid PEGs can be packaged in Kraft paper bags, polyethylene drums, or flexible intermediate bulk storage (FIBC).

Such different chemistries and processes would lead to different impurity profiles…

Other differences one may notice between POLYOX™ and PEG is in some of their applications. POLYOX™ has been used in the pharmaceutical industry in various applications as it possesses properties which make it ideal and unique for certain uses. It is a fast and high swelling polymer with low melting point. It has excellent mucoadhesive properties and is also a film former. In terms of processing, it does well in both wet and dry granulation applications, as well as direct compression. It is also an ideal polymer to be used in hot melt extrusion applications.

Its most widely known use is in Osmotic Pump technology (OPT). The high molecular weight grades, such as 301, COAG, and 303 are often used in the push layer, whereas the low molecular weight grades, such as N-10 and N-80, are used in the pull layer. Single layer osmotic have also used POLYOX™ grades in the past, where depending on the solubility of the active involved, some of the mid-molecular weight grades of POLYOX™ have been employed in this use.

Just like another widely used pharmaceutical Dow excipient, hydroxypropylmethyl cellulose (HPMC), POLYOX™ is a great choice for matrix formulations that require modified release. As the polymer wets and swells, it is able to control the release of the active from the entangled matrix. In another form of controlled release, POLYOX™ is also used in gastro-retentive systems, where the ingested tablet is required to swell to such a large size, that it is retained in the stomach for hours while the active is slowly released over time. Due to its water solubility, hydrophilicity, hydrogen bonding functionality, and good biocompatibility properties, POLYOX™ is

used in mucoadhesive applications, like bucal drug delivery. It is also used in film applications, primarily orally disintegrating film technology. It can be used in creams and gels, too.

PEG products have some similar applications, but it is mostly used as an active ingredient, binder, lubricant, solubilizer, or plasticizer in ointments, liquid suspensions, suppositories, and solid dosage oral forms. Interestingly, PEG can also be used as part of the synthesis of an active (PEGylation) which increases the size of an active molecule allowing it to move through the body at a slower rate. Such differences in applications would lead to slightly different amounts of product used in its final form. This is another reason why distinguishing between a PEG from a POLYOX™ grade is critical for the IID list.

Safety Profiles are the same for all grades of Polyethylene Oxide

PEO WSR N-10 and WSR 301 have been well-characterized in a series of reliable studies. WSR N-10 represents the lowest molecular weight and WSR 301 represents a high molecular weight in the PEO series of compounds. Data consistently indicates a lack of significant acute, subchronic, and chronic toxicity for both low and high molecular weight PEO compounds. This lack of toxicity is due to these materials having high molecular weights that characteristically cannot be absorbed through biological tissues such as the digestive tract or skin. Pharmacokinetics and metabolism studies confirm that both materials pass through the GI tract unchanged, and are excreted almost in entirety via the feces. Other studies on WSR N-10 indicate that it is non-mutagenic and is not a reproductive/developmental toxicant. Given the lack of toxicity, absorption, and metabolism of both low and high molecular weight PEOs, it is expected that intermediate weight PEOs would have essentially the same toxicological profile.

Organism	Test Type	Route	Reported Dose (Normalized Dose)	Effect	Source
Polyethylene Oxide WSR N-10 (100,000 daltons)					
Rat	LD50	Oral	>4000 mg/kg* (148,000 mg/m^2)	NOAEL	Nycum and Carpenter, 1968
Rabbit	LC50	Dermal	>2000 mg/kg* (74,000 mg/m^2)	NOAEL	Weil, 1969
Rat	3 month	Oral (diet)	>2350 mg/kg/d* (86,950 mg/m^2)	Increase in Female body weight and body weight gain; Increase in feed consumption; Relative adrenal weight in males; and increase in relative and absolute kidney and liver weight in females	Hermansky and Heese, 1992; Losco, 1992

Organism	Test Type	Route	Reported Dose (Normalized Dose)	Effect	Source
Rat	2-year	Oral (diet)	1150mg/kg/d* (42,550 mg/m^2)	Decrease body weight, body weight gain, and food consumption in males and females	Hermansky and Benson, 1995
Rat	Repro/ Devel	Oral (diet)	1540 mg/kg/d* (56,980 mg/m^2)	Decreased body weight change and feed consumption in males and increase in sperm motility	Blanset, 1998
Polyethylene Oxide WSR 301 (4,000,000 daltons)					
rat	LD50	Oral	>2000 mg/kg* (74,000 mg/m^2)	NOAEL	Nycum and Carpenter, 1968
Rabbit	LD50	Dermal	>400 mg/kg* (14,800 mg/m^2)	NOAEL	Nycum and Carpenter, 1968
Rat	3 month	Oral (diet)	<8100 mg/kg/d (299,700 mg/m^2)	Increase body weight gain in males; increased feed consumption in females; Histopathology: both males and females cloudy swelling in liver and kidney and albuminous precipitate in kidney	Weil and Carpenter, 1962b
Rat	2-year	Oral (diet)	2570 mg/kg/d* (101,750 mg/m^2)	Decrease relative liver weight in females: Histopathology: Males and females cloudy swelling in kidney; in males eosinophilic precipitate in kidney; and females cloudy swelling in liver	Weil and Carpenter, 1962b
Dog	2-year	Oral (diet)	596 mg/kg/d* (22,052 mg/m^2)	NOAEL	Weil and Carpenter, 1962a

*Highest dose Tested

POLYOX™ has been manufactured since the 1960s and it has been used and approved in numerous pharmaceutical products in the last 20 years. The previous version of the FDA IID contained many of its uses, including an overall approved dosage level of 543 mg. An excipient Drug Master File does exist for this product which contains all the key manufacturing information that FDA should need to do an appropriate review of an ANDA. With all of the already approved products in the market containing various grades of POLYOX™, there should be no question around adding POLYOX™ back into the IID list in a manner similar to what was in the IID before July 2011. Hopefully the differences between polyethylene glycol and polyethylene oxide have been sufficiently explained to warrant the addition of POLYOX™ into the list as its own separate entity using the compendial nomenclature “Polyethylene Oxide” as had been previously done with a maximum potency range of 543 mg.

EXHIBIT 5

- **Examples of inconsistencies - different viscosity "family" of polymers have the same toxicology profile regardless of viscosity grade.**

Inactive Ingredient	Route;	dosage form	CAS#	UNII	Max Potency
HPMC –Hypromellose/hydroxypropyl methylcellulose chemical composition differences are distinguished only by type, which is defined in compendia monographs, and are based on methoxy and hydropropoxy content. Viscosity is a physical parameter used to differentiate grades within a type.					
Hypromellose 2208 (15000 mPa.s)	ORAL	Capsule, sustained action, hard gelatin		Z78RG6M2N2	2.771 mg
Hypromellose 2208 (15000 mPa.s)	ORAL	Tablet, sustained action		Z78RG6M2N2	480 mg
Hypromellose 2208 (60000 mPa.s)	ORAL	Tablet, extended release		2F7T07H9ZD	175 mg
Hypromellose 2208 (80000 – 120000 mPa.s)	ORAL	Tablet, extended release	9004653	VM7F0B23ZI	54 mg
Hypromellose 2910 (15000 mPa.s)	ORAL-21	Tablet		288VBX44JC	0.75 mg
Hypromellose 2910 (15000 mPa.s)	ORAL	Tablet, enteric coated particles		288VBX44JC	445 mg
Hydroxypropyl methylcellulose 2906	ORAL	Tablet, film coated	9004653	Pending	[none]
Hydroxypropyl methylcellulose 2906	ORAL	Tablet	9004653	Pending	50 mg
Ethylcellullose – some listings have viscosity grade, others do not					
Ethylcellulose 20 mPa.s	ORAL	Tablet, extended release	9004573	BJG0S321QY	28.3048 mg
Ethylcellulose 50 mPa.s	ORAL	Tablet, extended release		6I475159RA	5.8728 mg
Ethylcelluloses	ORAL-28	Tablet		7Z8S9VYZ4B	1.05 mg
Ethylcelluloses	ORAL	Tablet, sustained action		7Z8S9VYZ4B	308.80 mg
Carboxymethylcellulose Sodium					
CMC Sodium	ORAL	Capsule, sustained action	9004324	K679OBS311	0.469 mg
CMC Sodium	ORAL	Capsule	9004324	K679OBS311	160 mg
CMC Sodium	ORAL	Tablet, coated	9004324	K679OBS311	2.2 mg
CMC Sodium	ORAL	Tablet	9004324	K679OBS311	48 mg
CMC Sodium	ORAL	Tablet, sustained action	9004324	K679OBS311	155 mg
Methylcellulose					
Methylcellulose	ORAL	Capsule, extended release	9004675	N/A	2.67 mg
Methylcellulose	ORAL	Tablet	9004675	N/A	183.6 mg